REMARKS

The instant invention relates in part to polyamide molecules comprising one or more amino acids containing N-methylpyrrole, 3-hydroxy-N-methylpyrrole, or N-methylimidazole moieties, and a positive patch consisting of a rigid group adjacent to a positive charged group. In certain embodiments, the rigid group of the polyamide molecule comprises a first amino acid of arginine, proline, lysine, or hydroxyproline, and a second amino acid of proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine, or hydroxyproline, respectively. Such molecules can provide sequence-specific binding within the minor groove of a DNA molecule, while presenting the positively charged group in an orientation that allows the polyamide molecule to disrupt interactions between proteins and the phosphate backbone or major groove of the DNA molecule.

Claims 1-26 are pending in the instant application. Applicants have amended claims 1, 3-19, 22, and 24-26 and canceled claim 2 herein. The amended claims do not introduce new matter or require a new search. Claim 1, as amended, incorporates the elements of dependent claim 2 into claim 1, while claim 22, as amended, corrects a typographical error. Applicants respectfully submit that the foregoing amendments comply with the Examiner's requirement and place the instant application in better form for appeal. Therefore, entry of the amendments at this time is therefor proper.

Notwithstanding the foregoing, Applicants expressly reserve the right to prosecute subject matter no longer or not yet claimed in the instant application or in one or more applications which may claim priority hereto. Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non-Art Related Remarks

The Examiner has objected to Claim 22 because of the presence of an unrecognizable letter. Applicants have amended the claim to correct this typographical error, and respectfully submit that the amendment renders the objection moot.

The Examiner has also objected to claims 2-19, asserting that the phrase "a polyamide of claim 1" is allegedly vague and indefinite because "[t]he use of the indefinite article "A" to begin

dependent claims renders the scope of the claims uncertain." Applicants respectfully traverse the objection.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added). *See also*, MPEP § 2173.02 (An examiner "should allow claims which define the patentable subject matter with a reasonable degree of particularity and distinctness.") (emphasis in original).

The skilled artisan would be reasonably apprised that the phrase the phrase "a polyamide of claim 1" in a dependent claim indicates that the claim refers back to and further limits claim 1, in accordance with 37 C.F.R. § 1.75. Applicants note that MPEP 608.01(n) specifically describes the use of the indefinite article in multiple dependent claims, and there is nothing of record to indicate that the skilled artisan would understand such language in the context of multiple dependent claims, but would somehow not understand the same language in a singular dependent claim.

Nevertheless, in an effort to advance prosecution, Applicants have amended the claims herein to recite the definite article, and respectfully submit that the rejection is rendered moot.

Art Related Remarks

35 U.S.C. §102

Claims 1, 5, 9, and 25-26 have been rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Bruice *et al.* Applicants respectfully traverse this rejection.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. Furthermore, the claims must be interpreted in light of the teaching of the specification. In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). *See also,* MPEP §2131.

As described in Applicants' previous response, the instant claims refer to polyamide molecules that comprise, amongst other elements, a positive patch consisting of a rigid group adjacent to a positively charged group. In paper No. 10, the Examiner contends that, because the compounds disclosed by the Bruice *et al.* publication "comprise at least two proline residues and an arginine type moiety bearing a positively charged guanidinium residue" (Paper No. 10, page 3, emphasis added), those compounds include the positive patch of the instant claims.

Applicants gratefully acknowledge the helpful discussion by telephone with the Examiner, who indicated that the reference to "proline residues" in the Office Action is in error, and that the Office Action should state that the Bruice *et al.* publication allegedly discloses compounds that "comprise at least two pyrrole residues and an arginine type moiety bearing a positively charged guanidinium residue."

Applicants respectfully submit that such a structure is not a positive patch as that term is defined in the instant specification. See, e.g., specification, page 17, line 16, through page 18, line 11.

Nevertheless, in an effort to advance prosecution, Applicants have amended claim 1 to better define the positive patch of the rejected claims. As amended, the claims refer to a rigid group comprising a first amino acid selected from amongst arginine, proline, lysine, and hydroxyproline, and a second amino acid selected from amongst proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine, and hydroxyproline.

Applicants respectfully submit that the Bruice *et al.* publication does not disclose any such polyamide molecules. Therefore, because Bruice *et al.* reference does not teach and suggest every limitation of the claimed invention, Applicants respectfully request that the rejection under 35 U.S.C. §102(b) be reconsidered and withdrawn.

Claims 1, 4-5, 9-12, 14, 16, 18, and 25-26 have been rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Swalley *et al*, Parks *et al.*, or Trauger *et al.* Applicants respectfully traverse this rejection.

Applicants gratefully acknowledge the helpful discussion by telephone with the Examiner, who indicated that the rejection is under 35 U.S.C. 102 § (a), and not under 35 U.S.C. 102 § (b) as mistakenly stated in the Office Action.

As discussed above, the rejected claims refer to polyamide molecules that comprise, amongst other elements, a positive patch consisting of a rigid group adjacent to a positively charged group, and the claims have been amended to better define the rigid group as comprising a first amino acid selected from amongst arginine, proline, lysine, and hydroxyproline, and a second amino acid selected from amongst proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine, and hydroxyproline.

It is respectfully submitted that the cited publications do not disclose a polyamide molecule comprising a positive patch as presently claimed. Therefore, since these references do not teach and suggest every limitation of the claimed invention, Applicants respectfully request that the rejection under 35 U.S.C. §102(a) be reconsidered and withdrawn.

35 U.S.C. §103

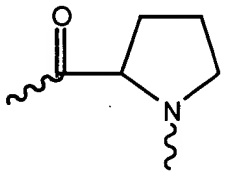
Claims 1, 2-8, 9-19 and 25-26 have been rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Swalley *et al.*; Parks *et al.* and Trauger *et al.* in view of Feng *et al.* Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also,* MPEP §2143.

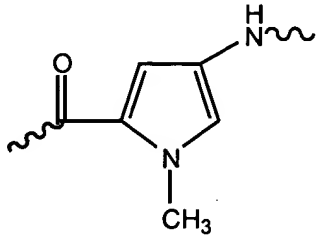
The Examiner contends that the instant claims "read on a polyamide comprising proline and arginine," and that Swalley *et al.*; Parks *et al.* and Trauger *et al.* publications allegedly disclose polyamides comprising N-methylimidazole and N-methylpyrrole. Whether or not this is true, Applicants respectfully disagree with the Examiner's conclusion that "[i]t would have been obvious to incorporate Arg-Pro-Arg into the polyamide compounds of those disclosed in the

cited references since the compounds of the prior art comprise amino acid moieties that are chemically and functionally similar to proline, namely N-methylpyrrole or arginine, positively charged N,N dimethylamino-propylamide, or histidine, namely N-methylimidazole." Paper No. 10, pages 4-5.

The skilled artisan would understand that proline is neither functionally nor structurally similar to N-methylpyrrole, as the Examiner asserts. For example, while proline is an unsaturated ring structure, the N-methylpyrrole ring comprises two double bonds; additionally, while proline in a polyamide is an α-amino acid linked through the ring nitrogen, N-methylpyrrole is not an α-amino acid and contains a methyl group at the ring nitrogen:

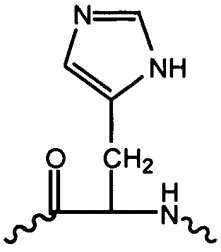


proline residue
in a polyamide

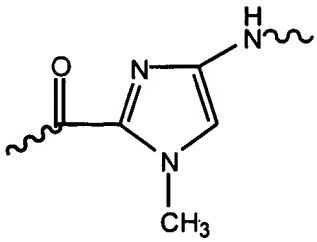


N-methyl pyrrole
residue in a polyamide

Similarly, the skilled artisan would also understand that histidine is neither functionally nor structurally similar to N-methylimidazole, as the Examiner asserts.



histidine residue
in a polyamide



n-methylimidazole
residue in a polyamide

Thus, one of ordinary skill in the art would recognize that, other than the presence of 5-membered rings in proline and pyrrole, and in histidine and N-methylimidazole, there are virtually no similarities between the molecules that the Examiner contends are "chemically and

functionally similar." Given the number of variables that must be selected and modified, and the nature and significance of the differences between the various molecules, and the absence of any indication in the Examiner's asserted *prima facie* case that such molecules would function in an equivalent manner to one another, there would be no motivation for the skilled artisan to incorporate Arg-Pro-Arg into the polyamide compounds of those disclosed in the cited references based on any alleged "chemical and functional similarity." *See*, MPEP § 2144.08(II)(A)(4) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound").

The Examiner also contends that the Swalley *et al.*; Parks *et al.* and Trauger *et al.* publications "do not teach polyamides wherein the positive patch comprises the amino acid sequence Arg_{140}-Pro_{141}-Arg_{142}," but that "Feng *et al.* disclose a polyamide compound which specifically interacts with the minor groove of DNA utilizing the sequence Gly-Arg-Pro-Arg at the carboxyl terminal domain." Paper No. 10, page 5. Again, whether or not this is true, Applicants respectfully disagree with the Examiner's conclusion that "[i]t would have been obvious to modify [the N-methylpyrrole and N-methylimidazole]polyamides with a sequence comprising Arg-Proline-Arg since polyamide compounds comprising these sequences are known to bind DNA with a high affinity in a sequence specific manner, [and] this modification would have broadened the sequence repertoire of these polyamide compounds for DNA recognition." Paper No. 10, page 5.

The skilled artisan would have understood from the Feng *et al.* publication that the sequence Arg-Pro-Arg in isolation from the larger Hin recombinase molecule would not provide any sequence-specific binding whatsoever. For example, the authors disclose that this 3 amino acid segment is part of a larger "amino terminal arm" that adopts an extended conformation to present the Gly_{139}-Arg_{140}-Pro_{141}-Arg_{142} portion in a proper manner to bind DNA. *See*, Feng *et al.*, page 351, left column. The authors also note the importance of Ile_{144} in maintaining this orientation. *Id.* Finally, the authors also note that "[s]pecific binding requires both major groove interactions involving a helix-turn-helix (HTH) α-helix motif and minor groove interactions involving the sequence Gly^{139}-Arg^{140}-Pro^{141}-Arg^{142}" (Id. at 348, right column), and not simply the Arg-Pro-Arg sequence in isolation as the Examiner suggests.

Thus, because it is only in the overall three-dimensional structure of Hin recombinase that these three amino acids have any role in "[binding] DNA with a high affinity in a sequence specific manner," one of ordinary skill in the art would not have had a motivation to select these three amino acids from Hin recombinase for grafting onto the polyamides disclosed in Swalley *et al.*; Parks *et al.* and Trauger *et al.* to provide the claimed invention. *See*, MPEP § 2144.08(II)(A)(4).

Moreover, the skilled artisan would expect a large number of proteins to include this identical stretch of amino acids, given the short length of the Arg-Pro-Arg sequence. For example, a BLAST search of the well known PIR database reveals that the sequence Arg-Pro-Arg is present in 10,639 known proteins, only one of which is cited by the Examiner to indicate that "polyamides with a sequence comprising Arg-Proline-Arg... are known to bind DNA with a high affinity in a sequence specific manner." Paper No. 10, page 5. Based on the fact that the artisan would expect a very large number of possible proteins to contain the sequence, this single protein using an Arg-Pro-Arg in a segment that binds DNA would lead the skilled artisan to understand that it is only in the context of the entire Hin recombinase three-dimensional structure that the sequence would have any role in "[binding] DNA with a high affinity in a sequence specific manner."

As discussed above, this understanding would be reinforced by the discussion in the Feng *et al.* publication itself, which indicates that multiple segments of the molecule are necessary to provide specific binding. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success in grafting these three amino acids onto the polyamides disclosed in Swalley *et al.*; Parks *et al.* and Trauger *et al.* to provide the claimed invention.

Applicants respectfully submit that, instead of carrying the burden of establishing a *prima facie* case of obviousness, the Examiner has fallen victim to "...decomposing an invention into its constituent elements, finding each element in the prior art, and then claiming that it is easy to reassemble these elements into the invention...". *In re Mahurkar*, USPQ2d 1801, 1817 (N.D. Ill. 1993). An obviousness determination cannot be premised on such an impermissible use of hindsight. *See, In re Fine*, 5 USPQ2d 1596 1600 (Fed. Cir. 1988) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references

of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against the teacher.")

Therefore, because there is no motivation provided to one of ordinary skill in the art to combine the cited references, and because one of ordinary skill in the art would not have had a reasonable expectation of success in making the suggested combination, no *prima facie* case of obviousness has been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

FOLEY & LARDNER

Dated: July 24, 2001

By: _____
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Appendix A: Marked-up claims, indicating amendments:

1. (Twice Amended) A polyamide molecule that specifically binds to base pairs in the minor groove of a DNA molecule, said polyamide molecule comprising:

one or more amino acids comprising a moiety selected from the group consisting of N-methylpyrrole, 3-hydroxy-N-methylpyrrole, and N-methylimidazole, wherein one or more of said amino acid(s) are not α-amino acids; and

a positive patch consisting of a rigid group adjacent to a positively charged group, said rigid group comprising a first and a second amino acid; said first amino acid being selected from the group consisting of arginine, proline, lysine, and hydroxyproline; and said second amino acid being selected from the group consisting of proline, glycine, serine, threonine, leucine, isoleucine, valine, alanine, and hydroxyproline.

3. (Amended) [A] The polyamide of claim 2 wherein said first amino acid is arginine and said second amino acid is proline.

4. (Amended) [A] The polyamide of claim 1 wherein the positively charged group comprises a synthetic or naturally occurring amino acid having a net positive charge.

5. (Amended) [A] The polyamide of claim 1 wherein said positively charged group is selected from the group consisting of a primary amino group, secondary amino group, tertiary amino group, quartenary amino group, guanidinium group, and an amidinium group.

6. (Twice amended) [A] The polyamide of claim 1 wherein said positively charged group is selected from the group consisting of arginine, lysine, and histidine.

7. (Amended) [A] The polyamide of claim 1 wherein said positively charged group is arginine.

8. (Amended) [A] The polyamide of claim 1 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

9. (Amended) [A] The polyamide of claim 1 wherein the polyamide has three or four carboxyamide binding pairs.

10. (Amended) [A] The polyamide of claim 1 wherein the polyamide comprises an (R)-2,4-diaminobutyric acid hairpin turn that facilitates specific binding to base pairs in the minor groove of a DNA molecule.

11. (Amended) [A] The polyamide of claim 10 wherein the R-2-amino group is derivatized to form an acid amide.

12. (Twice Amended) [A] The polyamide of claim 1 having the formula:

$$X_1X_2X_3\gamma X_4X_5X_6A$$

wherein γ is $-NH-CH_2-CH_2-CH_2-CONH-$ hairpin linkage derived from γ-aminobutyric acid or a chiral hairpin linkage derived from 2,4-diaminobutyric acid;

X_1/X_6, X_2/X_5, and X_3/X_4 represent three carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of 3-hydroxy-N-methylpyrrole/N-methylpyrrole (Hp/Py), N-methylpyrrole/3-hydroxy-N-methylpyrrole (Py/Hp), N-methylpyrrole/N-methylimidazole (Py/Im), N-methylimidazole/N-methylimidazole (Im/Py), and N-methylpyrrole/N-methylpyrrole (Py/Py) to correspond to the DNA base pair in the minor groove to be bound; and

A represents said positive patch consisting of a rigid group adjacent to a positively charged group.

13. (Amended) [A] The polyamide of claim 12 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

14. (Twice amended) [A] The polyamide of claim 1 having the formula:

$$X_1X_2X_3X_4\gamma X_5X_6X_7X_8A$$

wherein γ is –NH-CH_2-CH_2-CH_2-CONH- hairpin linkage derived from γ-aminobutyric acid or a chiral hairpin linkage derived from 2,4-diaminobutyric acid;

X_1/X_8, X_2/X_7, X_3/X_6, and X_4/X_5 represent four carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound; and

A represents said positive patch consisting of a rigid group adjacent to a positively charged group.

15. (Amended) [A] The A polyamide of claim 14 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

16. (Twice amended) [A] The polyamide of claim 1 having the formula:

$$X_1X_2X_3X_4X_5\gamma X_6X_7X_8X_9X_{10}A$$

wherein γ is –NH-CH_2-CH_2-CH_2-CONH- hairpin linkage derived from γ-aminobutyric acid or a chiral hairpin linkage derived from 2,4-diaminobutyric acid;

X_1/X_{10}, X_2/X_9, X_3/X_8, X_4/X_7, and X_5/X_6 represent five carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound; and

A represents said positive patch consisting of a rigid group adjacent to a positively charged group.

17. (Amended) [A] The polyamide of claim 16 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

18. (Twice amended) [A] The polyamide of claim 1 having the formula:

$$X_1X_2X_3X_4X_5X_6\gamma X_7X_8X_9X_{10}X_{11}X_{12}A$$

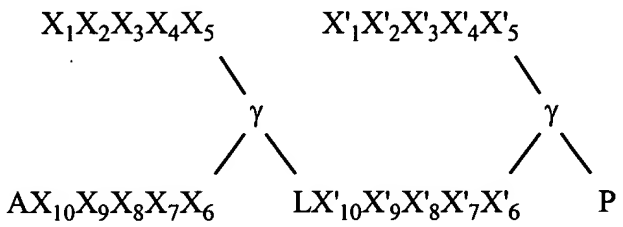
wherein γ is –NH-CH_2-CH_2-CH_2-CONH- hairpin linkage derived from γ-aminobutyric acid or a chiral hairpin linkage derived from 2,4-diaminobutyric acid;

X_1/X_{12}, X_2/X_{11}, X_3/X_{10}, X_4/X_9, X_5/X_8, and X_6/X_7 represent six carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of Hp/Py, Py/Hp, Py/Im, Im/Py, and Py/Py to correspond to the DNA base pair in the minor groove to be bound; and

A represents said positive patch consisting of a rigid group adjacent to a positively charged group.

19. (Amended) [A] The polyamide of claim 18 wherein the positive patch comprises the amino acid sequence Arg-Pro-Arg.

22. (Twice Amended) A tandem-linked polyamide having the formula:



wherein γ is - NH-CH_2-CH_2-CH_2-CONH- hairpin linkage derived from γ-aminobutyric acid or a chiral hairpin linkage derived from 2,4-diaminobutyric acid;

X_1/X_{10}, X_2/X_9, X_3/X_8, X_4/X_7, X_5/X_6, X'_1/X'_{10}, X'_2/X'_9, X'_3/X'_8, X'_4/X'_7, and X'_5/X'_6 represent carboxamide binding pairs which bind DNA base pairs and are selected from the group consisting of H_p/P_y, P_y/H_p, P_y/I_m, I_m/P_y, and P_y/P_y to correspond to the DNA base pair in the minor groove to be bound;

L represents an amino acid linking group selected from the group consisting of β-alanine and 5-aminovaleric acid (δ);

P represents a polyamide selected from the group consisting of $X_1X_2X_3\gamma X_4X_5X_6$, $X_1X_2X_3X_4\gamma X_5X_6X_7X_8$, $X_1X_2X_3X_4X_5\gamma X_6X_7X_8X_9X_{10}$, and $X_1X_2X_3X_4X_5X_6\gamma X_7X_8X_9X_{10}X_{11}X_{12}$, where X_1-X_{12} are independently selected from the group consisting of [∃-alanine]β-alanine, pyrrole, hydroxypyrrole and imidazole; and

A represents a positive patch consisting of a rigid group adjacent to a positively charged group.

24. (Amended) [A] The polyamide of claim 1 selected the group consisting of:

ImPyPyPy-γ-PyPyPyPy-β-RPR;

ImImPyPy-γ-ImPyPyPy-β-RPR;

ImPyPyPy-γ-PyPyPyPy-β-RPRRR;

ImImPyPy-γ-ImPyPyPy-β-RPRRR;

ImPyPyPy-γ-PyPyPyPy-β-R;

ImPyPyPy-γ-PyPyPyPy-β-RP;

ImPyPyPy-γ-PyPyPyPy-β-RGR;

ImPyPyPy-γ-PyPyPyPy-β-R^{D}PR;

ImPyPyPy-γ-PyPyPyPy-β-APR;

ImPyPyPy-γ-PyPyPyPy-β-KPR;

ImPyPyPy-γ-PyPyPyPy-β-RPK;

ImPyPyPy-γ-PyPyPyPy-β-C7-RPR; and

the pharmaceutically acceptable salts thereof.

25. (Amended) A method of inhibiting gene expression comprising contacting a regulatory sequence of a gene with [a] the polyamide of claim 1.

26. (Amended) A method of inhibiting gene expression comprising contacting a DNA molecule with [a] the polyamide of claim 1 whereby the DNA molecule is conformationally constrained.